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SUBJECT OF INVESTIGATION

RESPIRATORY DISEASES DUE TO

AIR POLLUTION

ON

TOKYO-YOKOHAMA AREA

II

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## ABSTRACT

In previous report, we informed that the respiratory symptoms were easily occurred among the people living in Tokyo-Yokohama area and their smoking habits as well as allergic constitution were closely correlated to the onset of such symptoms.

This time, main interest was subjected to whether air pollutants, such as sulfur dioxide etc., influence the onset of asthma attack in patients as well as experimental animals. In addition, the respiratory symptoms among the patients of chronic bronchitis were followed up so as to clarify the correlation between the incidence of them and the environmental factors related to the air pollution. The results of investigation are summarized as follows.

1. The influence of sulfur dioxide to guinea pigs was studied on the experimental asthma, measuring the respiratory sensitivity to acetylcholine. Exposures to 30 ppm sulfur dioxide seemed to increase the respiratory sensitivity to acetylcholine, though statistically not significant.

2. Pulmonary diffusing capacity for carbon monoxide was measured among asthmatic patients including similar type to T-Y asthma as well as normal individuals. No significant differences were detected among  $D_{LCO}$  of each group. Accordingly, it is suggested that there were no such changes among asthmatic patients including T-Y type as seen in the lung of emphysema or alveo-capillary block.

3. Patients with chronic bronchitis picked up from the previous survey were considered to be sensitive to the changes of air pollutants in the air, since the respiratory symptoms in them increased in parallel with the increase of air pollutants; i.e. dust fall, suspended particles and sulfur dioxide in the air.

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**FINAL REPORT      II**

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## INFLUENCE OF SULFUR DIOXIDE EXPOSURE TO EXPERIMENTAL ASTHMA IN GUINEA PIGS

Sulfur dioxide in the atmosphere of urban areas has been considered to be one of the causes of the increasing frequency of asthmatic attacks.<sup>1,3)</sup> The survey concerning the relationship between the concentration of sulfur dioxide in the atmosphere and the incidence rate of asthmatic attacks, which was presented in this report, has revealed that asthmatic attacks occurred frequently in condition of high atmospheric sulfur dioxide concentration in the Tokyo-Yokohama area.

In guinea pigs, a dyspneic state resembling human asthmatic attacks can be induced by the inhalation of an aerosol of acetylcholine (= Ach), and the mechanics of breathing during the attacks has been reported to be similar to man.<sup>2,4)</sup> Also, exposure to sulfur dioxide increases airway resistance in both man and guinea pig.<sup>1,4,11)</sup> This mechanism might account for the increased incidence of asthmatic attacks during conditions of high atmospheric concentration of sulfur dioxide, since airway obstruction is one of the main physiologic characteristics of asthmatic attacks. The purpose of this paper is to determine whether, in guinea pigs, the exposure to sulfur dioxide accelerates the experimental asthma induced by the inhalation of acetylcholine.

The respiration of guinea pigs was observed by recording the change in the pressure of the lung, which was opposite in sign to the pressure change in the body plethysmograph.<sup>3,6)</sup> The difference of bronchial sensitivity to Ach was compared between guinea pigs exposed to sulfur dioxide and others not exposed.

### MATERIALS AND METHODS

#### MATERIALS

Male guinea pigs, weighing 250g to 300 g, were used.

#### METHODS

1. Measurement of pressure change in the lung of guinea pigs (Recording of alveolar pressure tracing).

A guinea pig was placed in a comfortable sitting position in an air tight plastic cylinder (10cm in diameter and 20cm in length), and the pressure change in the cylinder was transmitted to a sensitive pressure transducer\*, carrier preamplifier\*\* and direct-writing recorder.\*\*\* Since the total amount of air in the plethysmograph-lung system is constant, an increase in air pressure inside the lungs of guinea pig, as during expiratory effort, must cause a decrease in pressure in the remainder of the gas in the plethysmograph. The resultant pressure change in the cylinder must be opposite in sign to the pressure change in the lung, i.e., the alveolar pressure change. Fig. I. shows the photograph of the apparatus.

Since alveolar pressure is almost equal to intrapleural pressure, the value of alveolar pressure was roughly estimated by comparing the cylinder pressure and the intrapleural pressure. The latter was transmitted to a pressure transducer\*\*\*\* by polyethylene catheter inserted into the pleural cavity.<sup>12)</sup> Fig. II. shows the pressure change in the body plethysmograph and that in the pleural cavity.

- \* Differential Pressure Transducer B, Nippon-Kohden-Kogyo Co.
- \*\* Sanborn Carrier Preamplifier, 350-1100b
- \*\*\* Sanborn Oscillographic Recording System, 964 (M)
- \*\*\*\* Differential Pressure Transducer, Nippon-Kohden-Kogyo Co.

## 2. Acetylcholine Inhalation Test in Guinea Pigs.

A saline solution of 10% acetylcholine ( W/V ) was diluted in 6 test tubes in serial doubling method. Before the test, an animal was placed in the body plethysmograph and the pressure change in the box, i.e., alveolar pressure change, was recorded continuously during the several respiratory cycles. An aerosol of the most dilute solution of acetylcholine was perfused through the plethysmograph box for 4 minutes. Immediately after the inhalation, the pressure change in the air tight box was measured. Increasing the concentration of acetylcholine solution, this procedure was repeated up to a sufficient concentration as to recognize the apparent pattern of dyspnea in the recording of the alveolar pressure tracing (the dyspneic pattern of alveolar pressure tracing will be described in the following paragraph). The minimal concentration of acetylcholine solution to cause dyspneic pattern in alveolar pressure curve was defined as "Respiratory Threshold to Acetylcholine" (RT-Ach).

During normal breathing, the alveolar pressure tracing was triangular or sine wave in form, 8) and the respiratory cycles were regular. During the dyspneic state induced by the inhalation of acetylcholine, alveolar pressure tracing was rather rectangular in form, i.e., steep and deep inspiratory descending slope followed by steep expiratory ascending slope and gently ascending expiratory plateau with rather long duration. The respiratory cycles became frequent and irregular. The change of the normal alveolar pressure tracing into a dyspneic one was, in most cases, relatively definite, as shown in Fig. III. In cases where the change in alveolar pressure tracing was not so definite, the animals were allowed to inhale aerosols of acetylcholine solution with higher concentration, and the previous change of the tracing was assured to be dyspneic, when the tracing recorded with these higher concentrations of acetylcholine showed the definite dyspneic pattern.

Aerosols of acetylcholine solutions were generated through a Vaponefrin nebulizer, using compressed oxygen with a flow rate of 6l per minute. Large particles of aerosols were excluded through a simple filter as shown in Fig. I., and the size of the particles of the aerosols ranged under 3 micra in aerodynamic diameter.

## 3. Exposure to Sulfur Dioxide

Guinea pigs were exposed to sulfur dioxide with concentrations of 100 and 30 ppm for the period of 30 minutes. Acetylcholine inhalation tests were carried out (1) immediately after the first exposure and (2) one day after the last exposure, the six daily consecutive exposures.

## RESULTS

The results were summarized in Fig. IV. and V.

### 1. The Change of RT-Ach of Guinea Pigs Exposed to 30 ppm SO<sub>2</sub> (Fig. IV.)

The mean RT-Ach of 15 guinea pigs was 5.36 mg/ml before the exposure, and after the first 30 minutes exposure the mean RT-Ach was 4.87 mg/ml, whereas the mean RT-Ach of 12 control guinea pigs were 4.35 mg/ml and 2.33 mg/ml at occasions before and after the exposures. The decrease of the mean RT-Ach of guinea pigs by the exposure was slightly less than that of the mean RT-Ach of controls in the corresponding period. This difference is not statistically significant.

The mean RT-Ach of 7 guinea pigs was 5.00 mg/ml before the exposure, and after the 6 daily consecutive exposures the mean RT-Ach was 1.89 mg/ml however the mean RT-Ach of 5 control guinea pigs were 4.35 mg/ml and 3.70 mg/ml on the occasions before and after the exposures. The decrease of the mean RT-Ach of guinea pigs by the consecutive exposures, was larger than that of the mean RT-Ach of the control in the corresponding period, though this difference proved not to be statistically significant.

An impression was given that the consecutive exposures of 30 ppm SO<sub>2</sub> might increase the respiratory sensitivity to Ach in guinea pigs.

## 2. The Change of RT-Ach of Guinea pigs Exposed to 100 ppm SO<sub>2</sub> (Fig. V.)

The mean RT-Ach of 5 guinea pigs was 4.35 mg/ml before exposure, and after the first 30 minutes exposure the mean RT-Ach was 5.75 mg/ml, whereas the mean RT-Ach of 5 control guinea pigs were 4.35 mg/ml and 3.70 mg/ml on the occasions before and after the exposure. The mean RT-Ach of exposed guinea pigs increased slightly by the exposure, and the mean RT-Ach was relatively unchanged for the corresponding period. This difference in the changes of RT-Ach between the treated and control groups is not statistically significant.

The mean RT-Ach of 13 guinea pigs was 2.62 mg/ml before the exposures, and after the 6 consecutive exposure the mean RT-Ach was 2.03 mg/ml, whereas the mean RT-Ach of 4 control guinea pigs were 5.00 mg/ml and 4.06 mg/ml on the occasions before and after the exposures. The mean RT-Ach of both treated and control guinea pigs were almost unchanged for the period of the experiment.

Before Ach inhalation test, 4 guinea pigs which had been exposed to SO<sub>2</sub> consecutively, showed alveolar pressure tracing patterns relatively similar to that of dyspnea. One guinea pig without SO<sub>2</sub> exposure showed the same phenomenon. These 4 guinea pigs, except 1, showed lowered RT-Ach, and some of them were found to have patchy consolidations in the lungs at autopsy.

## DISCUSSION

In the previous contractor's report and following publications<sup>5,9,10</sup> Miyamoto et al. <sup>7)</sup> have found that exposure to SO<sub>2</sub> made guinea pigs more sensitive to inhaled Ach, i.e., the inhalation of lower concentration of Ach solution was sufficient to produce respiratory distress in the animals. In that experiment, the respiratory distress meant respiratory symptoms such as prolongation of expiration, tachypnea, irregularity of respiratory rhythm, frequent sneezing, etc..

In this experiment, experimental asthmatic attack was defined as the dyspneic state showing definite change of alveolar pressure tracing from sine or triangular wave to rectangular one. And, no significant effects of SO<sub>2</sub> inhalation were found upon the experimental asthma, though consecutive



inhalation of relatively low concentration of  $\text{SO}_2$  seemed to decrease the RT-Ach, i.e., to provoke experimental asthma more easily. On the other hand, one time exposure to  $\text{SO}_2$  had no definite influence on the experimental asthmatic attacks at all.

The results of the previous and present reports suggest that the exposure to  $\text{SO}_2$  increases bronchial irritability to Ach, causing tachypnea, sneezing and irregularity of respiratory rhythm, whereas the exposure might have relatively less influence on the occurrence of apparent experimental asthmatic attacks in guinea pigs.

Our previous report suggested that the polluted atmosphere of the Tokyo-Yokohama area increases the incidence of respiratory symptoms, coughing, sputum production, throat irritation and pulmonary function disturbances, while there was no increased incidence of airway obstructive diseases.

It was reported that there was no significant difference in the incidence of infantile asthma among the children living in the air-polluted area and in non-polluted. <sup>2)</sup> If bronchial asthma was produced by continuous bronchial irritation, the incidence of the disease should be higher in the air-polluted, industrialized area, such as the T-Y area.

The present experiment and the previous survey suggest that the pollution of the air might be one of the aggravating factors of bronchial asthma but have little part in etiology.

The method employed in this experiment was the observation of alveolar pressure tracing, and was not sensitive enough to detect the more subtle changes of air way obstruction induced by  $\text{SO}_2$  and / or Ach inhalations. At present an attempt to measure airway resistance of guinea directly is going on and the more detailed study of this theme will be carried out later.

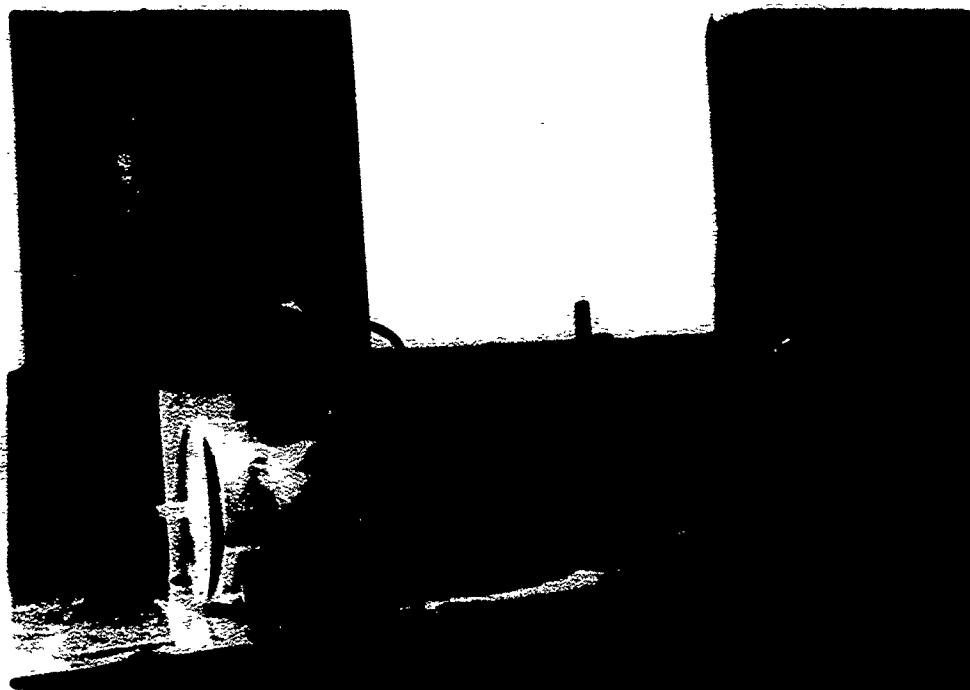
#### SUMMARY

The influence of sulfur dioxide exposure to experimental asthmatic attacks was studied in guinea pigs, measuring the respiratory sensitivity to acetylcholine. No significant change of respiratory threshold to acetylcholine ( RT-Ach ) was observed among the groups exposed to various concentrations of sulfur dioxide, though an impression was given that consecutive exposures to 30 ppm sulfur dioxide might increase the respiratory sensitivity to acetylcholine.

The roles of sulfur dioxide exposure were discussed in relation with experimental asthma in guinea pigs and bronchial asthma in man.

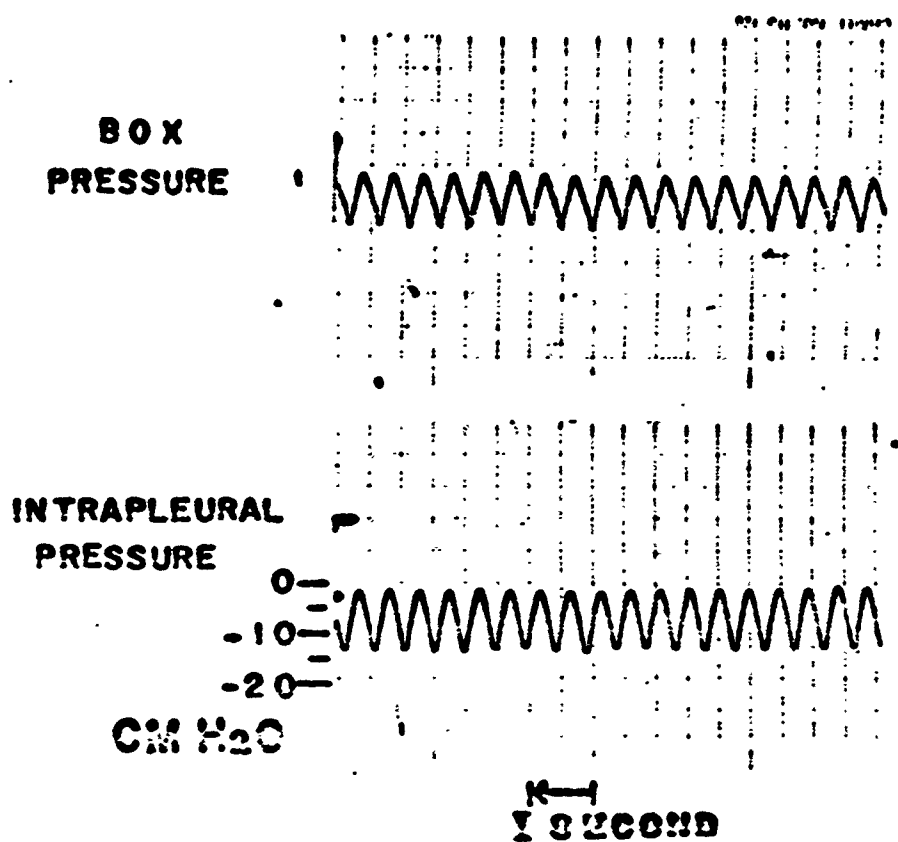
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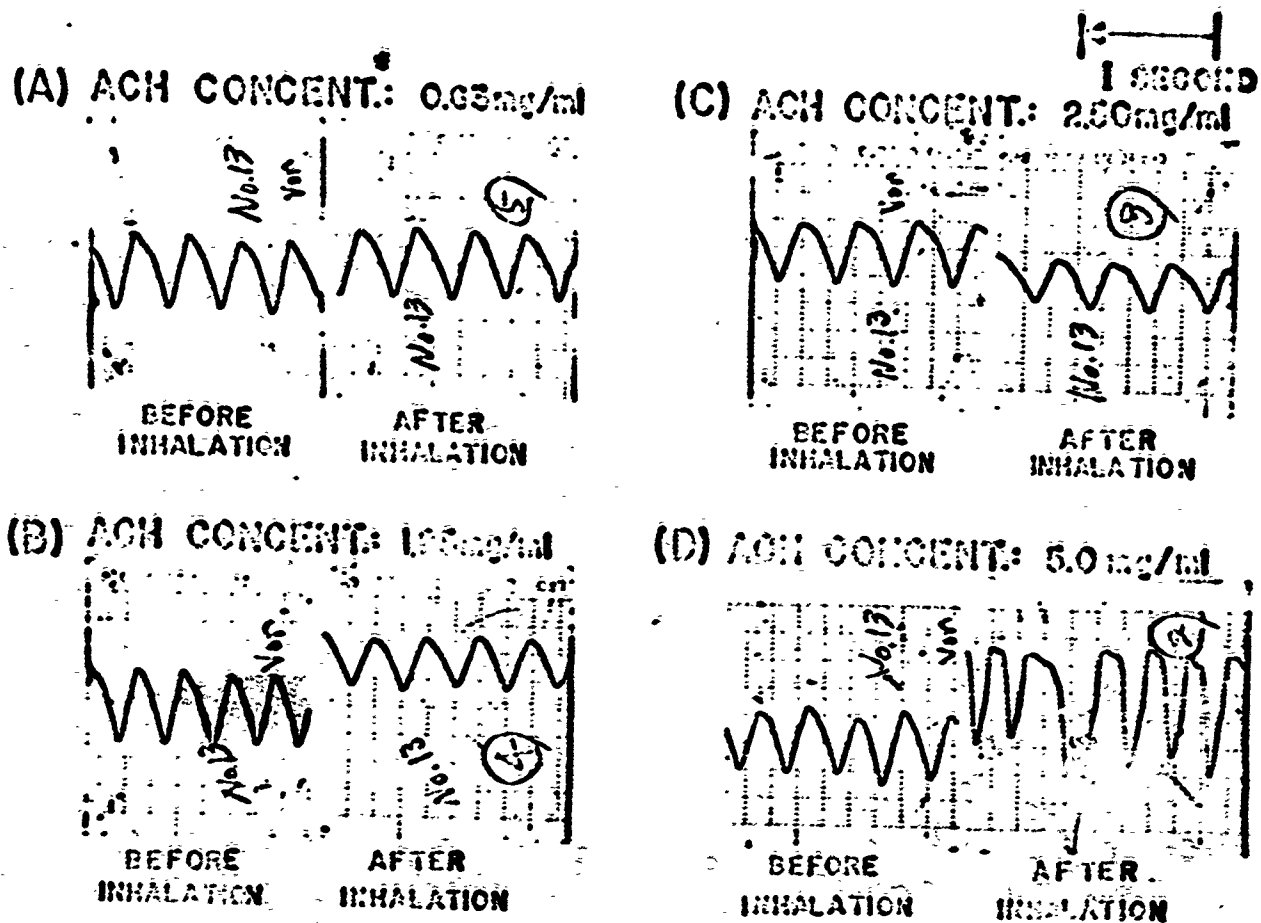
**Fig. I.      Photograph of Apparatus**

**A guinea pig is placed in body plethmograph. Upper tubing connects to the pressure transducer. One side-tubing connects to the nebuliser and the filter. The other side-tubing is for exhaust. On recording alveolar pressure tracing, both side-tubings are closed.**



**Fig. 11. Sample Tracing of Guinea Pig Respiration.**

**Simultaneous Recording of Box Pressure and Intrapleural Pressure.**

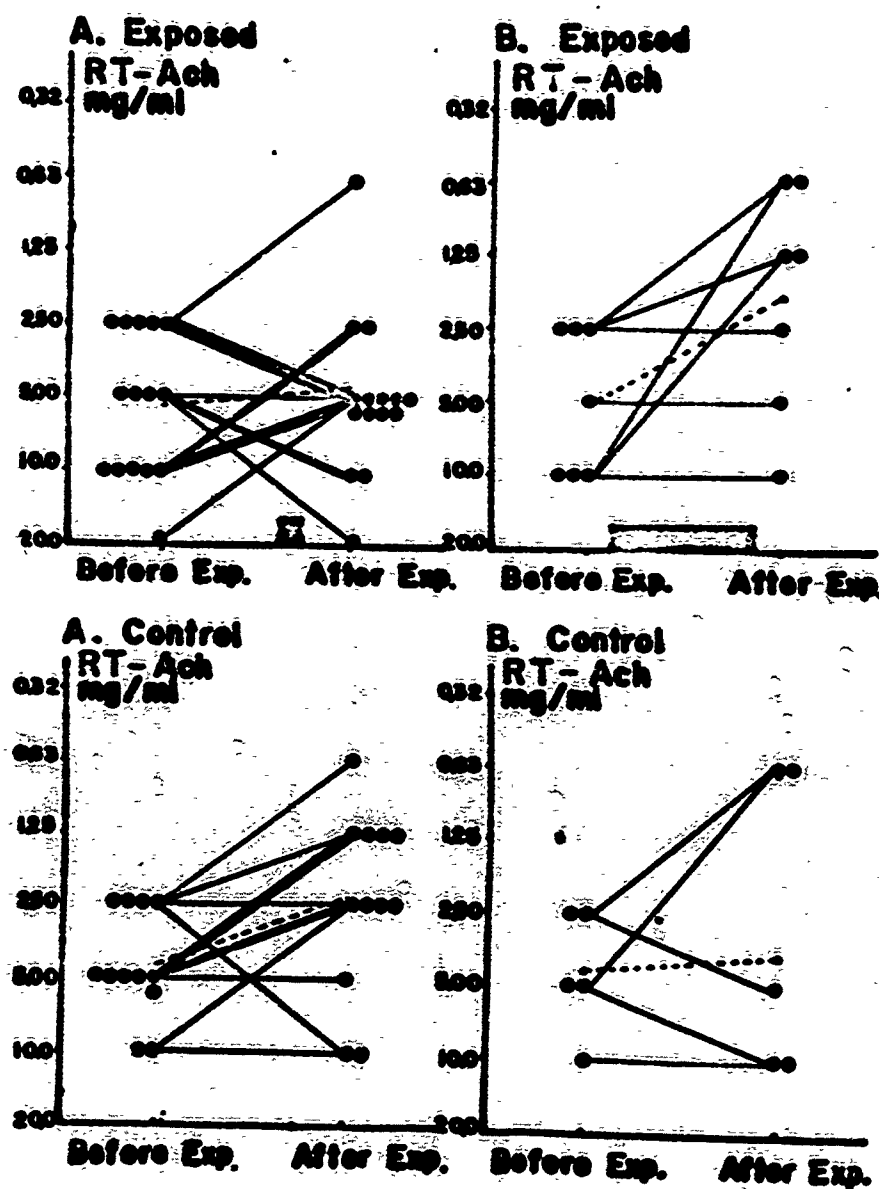


**Fig. III. Sample Tracing of Guinea Pig Respiration in Ach Inhalation Test.**

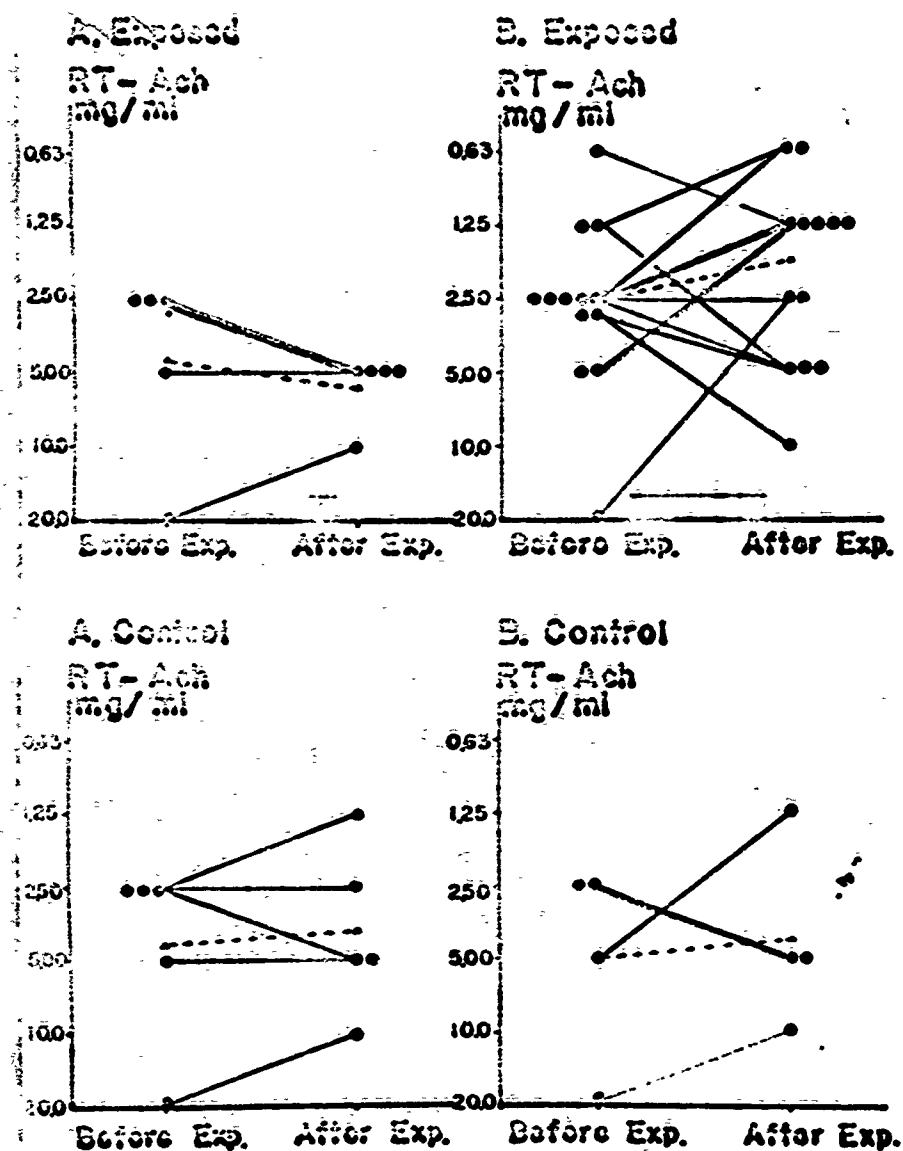
In ( A ), ( B ) and ( C ), the guinea pig breathed normally after the inhalation of an aerosol of Ach solution, and no significant change of alveolar pressure tracing was observed.

In ( D ), the guinea pig became dyspneic during the inhalation, and the alveolar pressure tracing showed the typical dyspneic pattern.

\* The concentration of acetylcholine solution ( W/V ) used for the test.



**Fig. IV. Change of Respiratory Threshold to Acetylcholine in Guinea Pigs after Exposure of 30 P.P.M. Sulfur Dioxide.**  
 ( A ) Immediately after the First Exposure.  
 ( B ) One Day after the 6 Daily Consecutive Exposures.



**Fig. V. Change of Respiratory Threshold to Acetylcholine in Guinea Pigs after Exposure of 100 P.P.M. Sulfur Dioxide.**  
 ( A ) Immediately after the first Exposure.  
 ( B ) One Day after the 6 Daily Consecutive Exposures.

## PULMONARY DIFFUSING CAPACITY IN ASTHMATIC PATIENTS WITH AND WITHOUT CLINICAL FEATURES OF "SO-CALLED TOKYO-YOKOHAMA ASTHMA"

In 1954, a new environmental respiratory disease, so-called Tokyo-Yokohama asthma, was reported,<sup>3)</sup> and the air pollution of this area was assumed to be a contributing factor.<sup>3)</sup> The possibility has been suggested that this "Tokyo-Yokohama asthma (TY-A)", under certain condition, progresses rapidly to emphysema.<sup>8,10)</sup>

In our previous report, we concluded that air pollution in T-Y area is harmful to the respiratory tract, indicated by increasing respiratory symptoms and disturbing pulmonary functions.<sup>7)</sup> The total of 237 asthmatic patients from our clinic were investigated. These investigations revealed no cases presenting characteristics compatible with the entity of the so-called T-Y asthma, though some presented quite similar pictures.<sup>8)</sup>

In this study, pulmonary diffusing capacity of carbon monoxide was measured among the asthmatic patients with one or more of clinical features of so-called T-Y asthma and without them.

Pulmonary diffusing capacity is frequently reduced in chronic obstructive emphysema, due to destruction of the alveolar and capillary walls, decreasing the surface area for gas change. In uncomplicated bronchial asthma, the diffusing capacity is relatively normal.<sup>1,2,11)</sup>

The present investigation was aimed at knowing if, measuring the pulmonary diffusing capacity, emphysematous changes would be suggested among the asthmatic patients having symptoms similar to T-Y asthma.

### SUBJECTS AND METHODS

The asthmatic patients studied were in- and out-patients in the Department of Physical Therapy and Medicine, Tokyo University Hospital, who had episodes of paroxysmal dyspnea and wheezing without apparent other respiratory diseases. Eight of them presented the history and/or clinical features similar to T-Y asthma, i.e., the initial experience of asthmatic attacks in T-Y area after their move to this industrialized area from rural areas, relief of asthmatic attacks by the removal from air-polluted T-Y area, and exacerbation by the return to T-Y area. They were composed of 5 males and 3 females, with the mean age of 25.9 (SD  $\pm$  7.2), ranging from 17 to 40 years of age. Thirty of the asthmatic patients, 23 males and 7 females, presented neither history nor clinical features similar to T-Y asthma. The age of these subjects ranged from 15 to 64 years of age, with the mean of 34.1 (SD  $\pm$  13.9). Sixteen normal subjects, 10 males and 6 females, were physicians or technicians in Tokyo University Hospital. The age of these subjects ranged from 17 to 43 years of age, with the mean of 25.4 (SD  $\pm$  7.7).

Pulmonary diffusing capacity was measured by Forster's single breath carbon monoxide method as modified by Ogilvie and co-workers.<sup>6)</sup> The measurements were made with a Collins box-balloon respirometer with a 5-way Rudolph valve. The inspired test gas contained approximately 0.2 percent carbon monoxide, 10 percent helium, 21 percent oxygen, and the balance nitrogen. The breathholding period was about 10 seconds, and an effort was made to collect the expired gas as fast as possible. The carbon monoxide and helium were analyzed in the Godart infra-red CO analyzer and the Godart pulmoanalyzer respectively. The diffusing capacity values presented in this paper represent



(1)  $D_{LCO}$ : milliliters of carbon monoxide transferred per minute per each millimeter of mercury pressure for carbon monoxide, (2) Krogh's coefficient ( $K_{CO}$ ) per minute.\* The latter coefficient was used because many of the asthmatic patients showed increased alveolar volume and consequently there was the possibility that their  $D_{LCO}$  were over-estimated.

The diffusing capacity measurements were carried out during the period of remission from asthmatic symptoms, and the subjects were checked to be sure that they were free from asthmatic symptoms before the test.

The chest X-ray films of asthmatic patients were reviewed for the presence of emphysematous change, i.e., increased transparency of lung field, widening of bony thoracic cage, lowering of the diaphragm, decreased vascular markings etc. The findings of the chest X-ray films were roughly divided into 4 categories, i.e., normal, mildly, moderately, and severely emphysematous.

\*  $K_{CO}$  was calculated from  $D_{LCO}$  following the equation:  $K_{CO} = D_{LCO} \times (BP - 47) / V_A$ , where BP is barometric pressure represented in millimeters of mercury pressure, and  $V_A$  is alveolar volume represented in milliliters.

## RESULT

Table I. summarizes the values for the pulmonary diffusing capacity, other pulmonary function tests and brief history for the asthmatic patients similar to T-Y asthma.

Fig. I. and Fig. II. show  $D_{LCO}$  and  $K_{CO}$  among the asthmatic patients similar to T-Y asthma, asthmatic patients of ordinary type and normal subjects. The mean  $D_{LCO}$  in the asthmatic patients similar to T-Y asthma was  $34.3$  ( $SD \pm 5.3$ ) ml/min./mmHg, compared with the mean  $D_{LCO}$  of  $32.4$  ( $SD \pm 9.0$ ) ml/min./mmHg in asthmatic patients of ordinary type, and of  $29.4$  ( $SD \pm 5.8$ ) ml/min./mmHg in normal subjects. There is no statistically significant difference among these mean values at the 5 percent level. The mean  $K_{CO}$  in asthmatic patients similar to T-Y asthma was  $5.92$  ( $SD \pm 1.40$ ) min.<sup>-1</sup>, compared with the mean  $K_{CO}$  of  $5.45$  ( $SD \pm 1.34$ ) min.<sup>-1</sup> in asthmatic patients of ordinary type, and of  $5.04$  ( $SD \pm 0.61$ ) min.<sup>-1</sup> in normal subjects. There are no statistically significant differences among these mean values at the 5 percent level.

Fig. III., Fig. IV. and Fig. V. show  $D_{LCO}$  plotted against  $\%FEV_{1.0}/FVC$ , RV/TLC ratio and TLC /Predicted TLC ratio among the asthmatic patients similar to T-Y asthma and ordinary ones. Individual points of asthmatic patients similar to T-Y asthma were included in the range of ordinary asthmatic patients in each of the figures. The mean  $\%FEV_{1.0}/FVC$  in asthmatic patients similar to T-Y asthma was  $69.5$  ( $SD \pm 10.2$ )%, compared with the mean  $\%FEV_{1.0}/FVC$  of  $63.6$  ( $SD \pm 16.2$ )% in ordinary asthmatic patients. There is no statistically significant difference between the mean values. The mean RV/TLC ratio in asthmatic patients similar to T-Y asthma was  $28.6$  ( $SD \pm 6.3$ )%, compared with the mean RV/TLC ratio of  $37.2$  ( $SD \pm 9.5$ )% in ordinary asthmatic patients. This difference is statistically significant at the 5 percent level. The mean TLC /Pred. TLC ratio in asthmatic patients similar to T-Y asthma was  $116.5$  ( $SD \pm 12.0$ )%, compared with the mean ratio of  $127.3$  ( $SD \pm 23.0$ )%, in ordinary asthmatic patients. There is no statistically significant difference between the mean values at the 5 percent level.

Fig. VI. summarizes the review of the chest X-ray films. This results revealed that asthmatic patients similar to T-Y asthma presented relatively slight emphysematous changes on chest X-ray films.

## DISCUSSION

Significant decrease in diffusing capacity are invariably seen in patients with advanced chronic obstructive emphysema. It is believed that this decrease is related to the loss of pulmonary vascular bed. Also, it is suggested that differential diagnosis between bronchial asthma and chronic obstructive emphysema can be established by the presence of a normal diffusing capacity in asthma as compared with a low diffusing capacity in emphysema.<sup>1,2, 11)</sup>

One might speculate that some noxious agents contained in the air of an industrialized area might cause an alveo-capillary block, especially, among asthmatic patients, who might be sensitized and whose lung might be susceptible to non-specific stimuli.

Diffusing capacity in asthmatic patients similar to T-Y asthma, like the ordinary type, was found to be within the normal range or more. These results showed that, as far as pulmonary diffusing capacity was concerned, bronchial asthma similar to T-Y asthma was identical to ordinary bronchial asthma, and suggested that there were neither the changes of lung as seen in chronic obstructive emphysema nor in alveo-capillary block.

Diffusing capacity in bronchial asthma similar to T-Y asthma was relatively high compared with that of ordinary type, though not significant. This difference could be explained by the short duration of the disease in the former, since diffusing capacity in bronchial asthma has tendency to decrease in the course of the disease.<sup>5)</sup>

The mean  $\dot{V}E_{V_{50}}/FVC$  of asthmatic patients similar to T-Y asthma was larger than that of ordinary ones, and the mean  $RV/TLC$  ratio and the mean  $TLC/\text{predicted } TLC$  ratio were lower among the asthmatic patients similar to T-Y asthma than of ordinary type. These differences could be explained by the shorter duration and younger age among the former. From these results, it can not be proved that asthmatic patients similar to T-Y asthma have particular tendency to show obstructive or hyperinflation changes in their lungs, compared with ordinary asthmatic patients.

Individual points plotted in Fig. III, IV and V of the asthmatic patients similar to T-Y asthma represented by  $D_{LCO}$  and  $\dot{V}E_{V_{50}}/FVC$ ,  $D_{LCO}$  and  $RV/TLC$  ratio of  $TLC/\text{predicted } TLC$  ratio, were all in the range of those of the ordinary asthmatic patients. These results, too, show that asthmatic patients similar to T-Y asthma can not be said to form a particular group different from those of ordinary type.

By performing pulmonary function test including  $CO$  diffusing capacity,  $\dot{V}E_{V_{50}}/FVC$ ,  $RV/TLC$  ratio and  $TLC/\text{predicted } TLC$  ratio, we could find no significant differences between the mean values of the asthmatic patients who had had their initial asthmatic attacks after their move to Tokyo-Yokohama area or whose move to T-Y area aggravated their asthmatic symptoms, and of the ordinary asthmatic patients. The asthmatic patients selected for their similarity to so-called "T-Y asthma" are ordinary asthmatic patients who only started their initial attacks in T-Y area, and have no changes that suggest emphysema, especially chronic obstruction emphysema, as compared to the other asthmatic patients.

## SUMMARY

Pulmonary diffusing capacity for carbon monoxide was measured among asthmatic patients similar to T-Y asthma, asthmatic patients of the ordinary type and normal subjects. No significant differences were detected among the mean diffusing capacity values of each group. The results suggested that, in bronchial asthma similar to T-Y asthma, like in ordinary bronchial asthma, there were neither destructive changes as seen in the lung of chronic obstructive emphysema nor alveo-capillary block.

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Table 1. Pulmonary Diffusing Capacity and Other Pulmonary Functions in Eight Asthmatic Patients with Clinical Features Similar to T-Y Asthma.

Subject	Sex	Age	Disease Duration (years)	Emphysematous Change in Chest X - Ray Film	D <sub>LCO</sub>	K <sub>CO</sub>	%FEV <sub>1.0</sub> /VC	%RV/TLC	% TLC		
No.	(years)	(m <sup>2</sup> )	(years)	(nl/min./mmHg) (min. <sup>-1</sup> )	(percent)	(percent)	(percent)	(percent)	(percent)		
1	IN	M	29	1.58	2	slight	41.0	5.32	77	30.8	140
2	KS	M	30	1.54	1	none	38.0	5.70	75	23.2	119
3	SI	M	17	1.73	3	moderate	37.0	6.04	60	28.6	129
4	TR	M	30	1.47	3	moderate	28.3	5.01	58	47.4	130
5	HT	F	19		4	slight	42.3	7.18	60	39.5	102
6	WK	F	22	1.49	1	none	38.5	8.86	86	25.4	105
7	YM	M	20	1.59	3	slight	31.0	5.32	61	21.5	147
8	TY	F	40	1.54	1	slight	18.4	3.95	79	31.9	114
Mean Value		25.9	2.3		34.3	5.92	70	28.6	117		
(Standard Deviation)					(SD ± 5.3)	(SD ± 1.40)	(SD ± 10.2)	(SD ± 6.3)	(SD ± 12)		

#### History and Clinical Features

1. Initial asthmatic attacks accompanied with persistent cough, on May, 6 years after his move to Tokyo and then, to Kawasaki.
2. Initial asthmatic attacks, on Oct., 6 months after his move to Tokyo from Fukuoka-Profecture.
3. Initial asthmatic attacks, on Nov., 5 months after his move to Tokyo.
4. Initial asthmatic attacks, on Sept., 8 months after his move to Tokyo.
5. Pt. was born in Tokyo, and moved to a rural area at 2 years of age. Initial asthmatic attacks, on Feb., 2 years after her return to Tokyo.
6. Initial asthmatic attacks, in winter, 3 days after her move to Tokyo. Asthmatic attacks had been frequent in winter.
7. Pt. had initial asthmatic attacks in a rural city of Kanto-plain. His move to Tokyo had aggravated his asthmatic symptoms, and his removal from Tokyo frequently alleviated the symptoms.
8. Initial asthmatic attacks, on Nov., 1 year after her move to Tokyo.

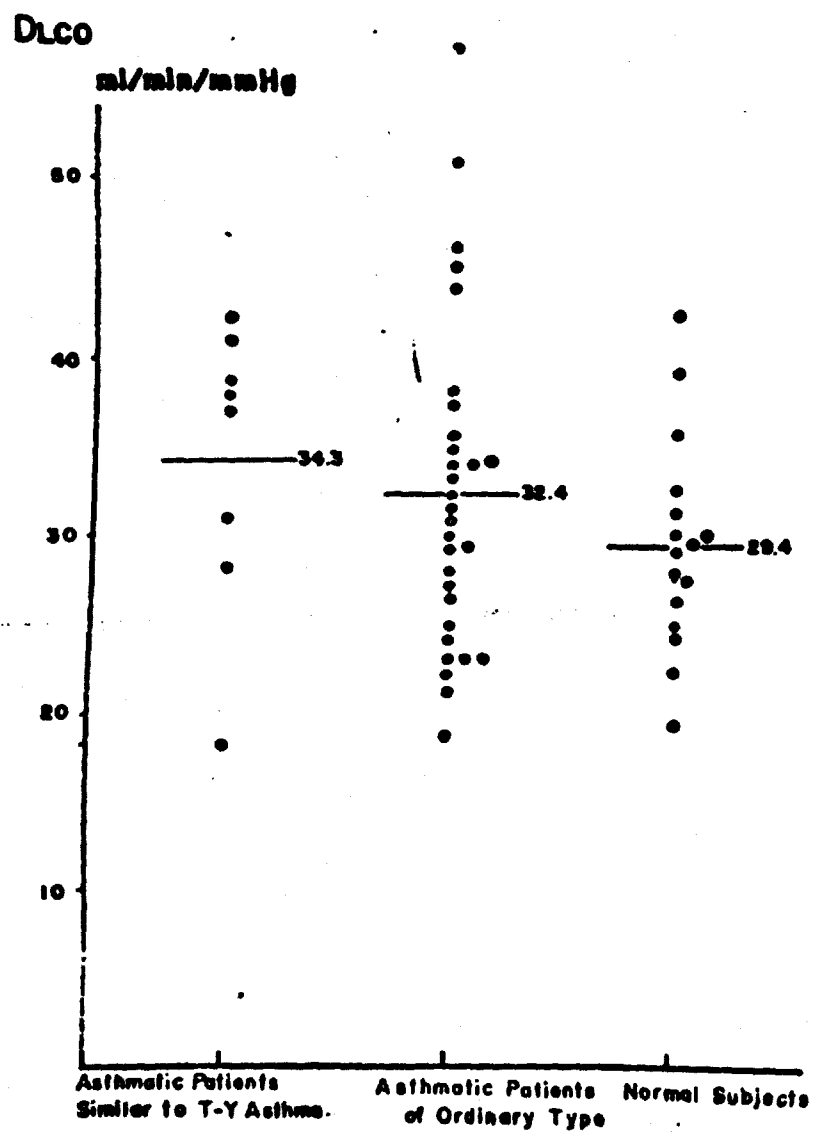


Fig. I. DLCO in Each Group.

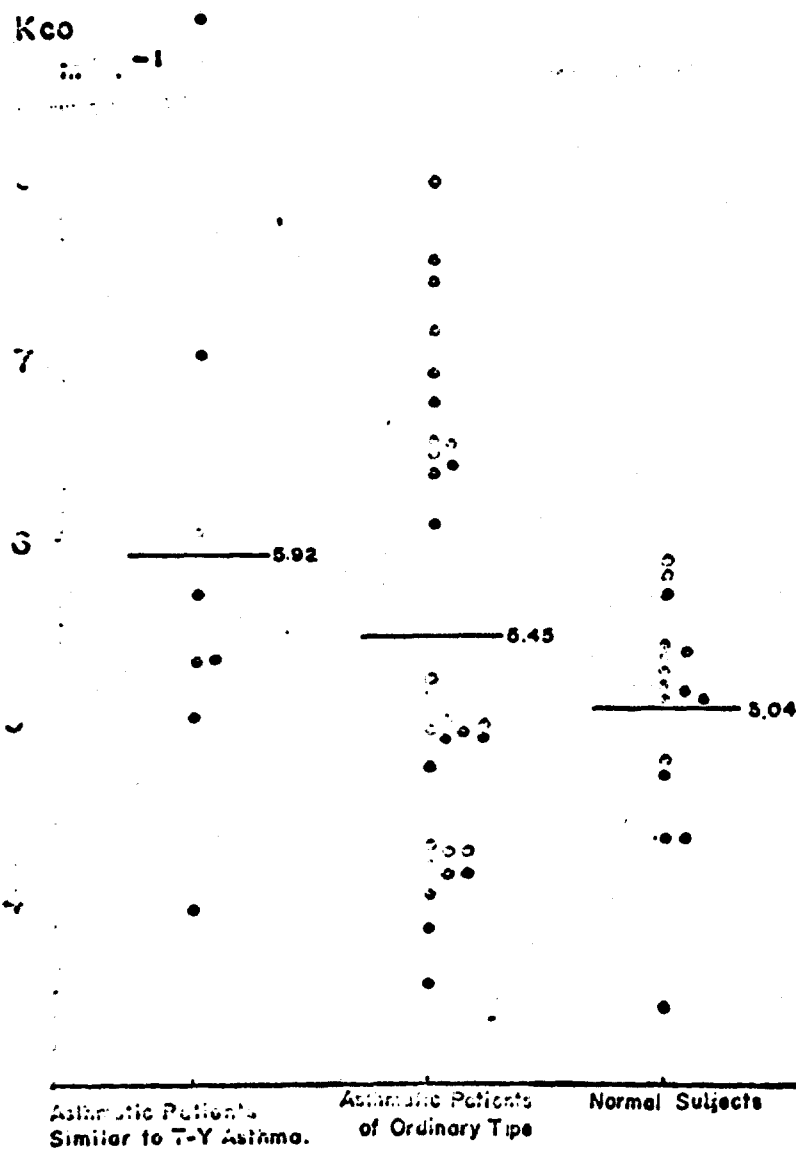


Fig. II. Krogh's Coefficient ( $K_{CO}$ ) in Each Group.

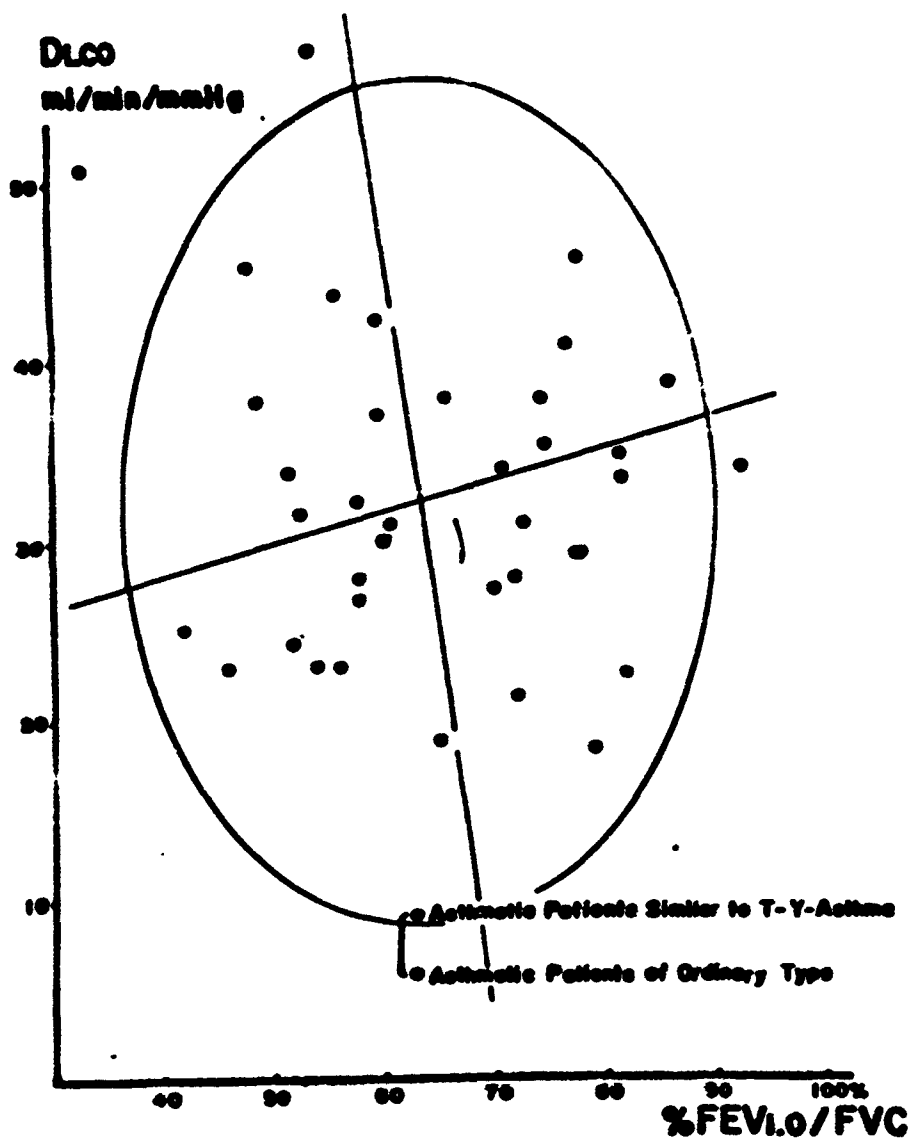


Fig. III.  $DL_{CO}$  Plotted against  $\%FEV_{1.0}/FVC$ , among Asthmatic Patients Similar to T-Y Asthma and of Ordinary Type.

Individual points outside the ellipsoid may well be said not to be included in the group of asthmatic patients of ordinary type at the 5% level of significance.



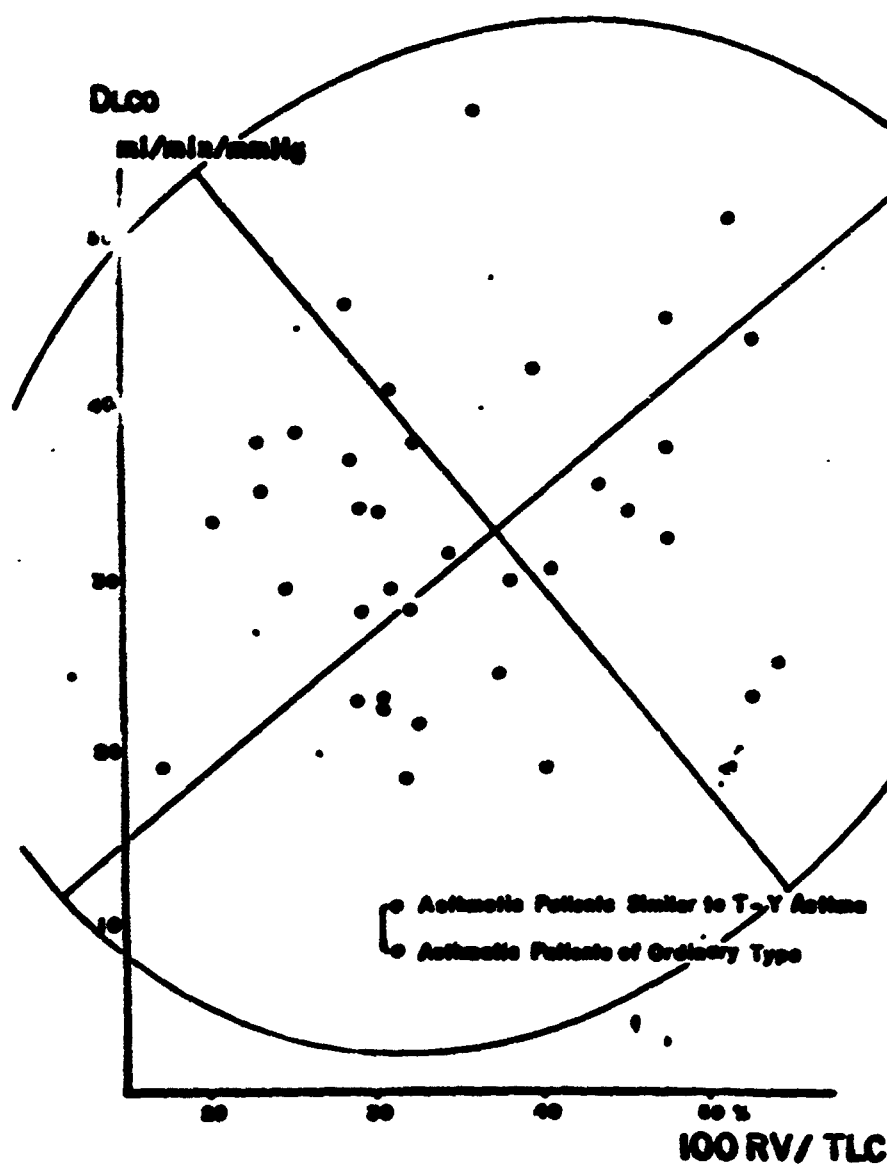


Fig. IV.  $D_{100}$  Plotted against  $\text{RV} / \text{TLC}$  Ratio, among Asthmatic Patients Similar to T-Y Asthma and of Ordinary Type.

Individual points outside the ellipsoid may well be said not to be included in the group of asthmatic patients of ordinary type at the 5 percent level of significance.

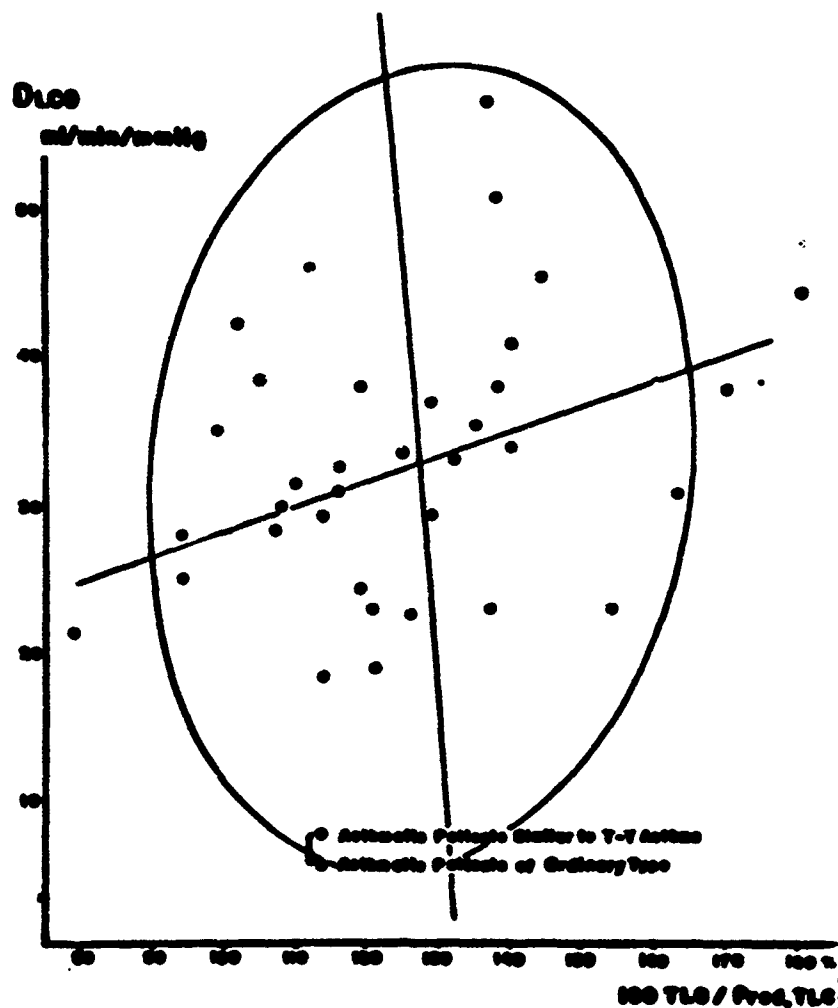
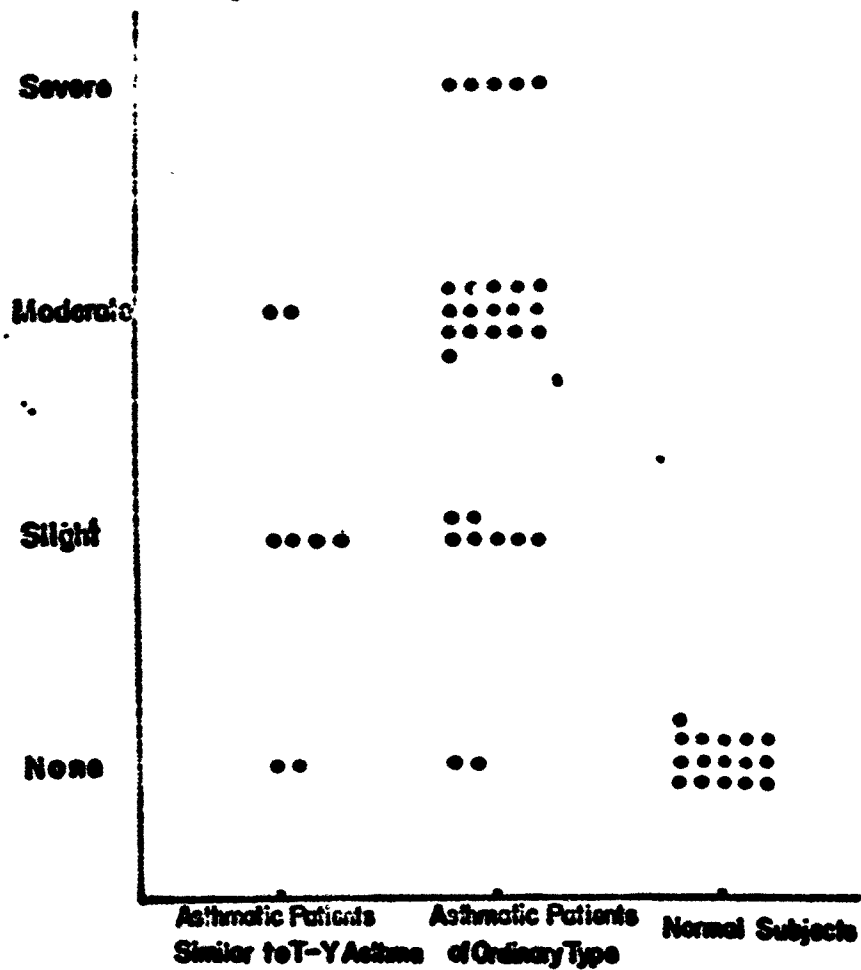


Fig. V.  $D_{100}$  Plotted against TLC / Pred. TLC Ratio, among Asthmatic Patients Similar to T-Y Asthma and of Ordinary Type.

Individual points outside the ellipsoid may well be said not to be included in the group of asthmatic patients of ordinary type at the 5 percent level of significance.

**Emphysematous changes  
in Chest X-Ray Films**



**Fig. VI. Emphysematous Changes in Chest X - Ray Films in Each Group.**

## FOLLOW UP STUDY OF THE DAILY INCIDENCE OF RESPIRATORY SYMPTOMS IN THE GROUP HAVING CHRONIC BRONCHITIS

In the previous reports, we have informed on the results concerning with the incidence of respiratory symptoms in male workers of a factory of Tokyo-Yokohama area which were compared with that of a rural area, and also have informed on the study of asthma patients in Tokyo-University Hospital Clinic.<sup>5,6)</sup> Further study was subjected to the follow up of daily incidence of respiratory symptoms in the group of chronic bronchitis picked up from the subjects in the previous survey.

About hundred patients were chosen through the criteria of chronic bronchitis indicated by Fletcher<sup>3)</sup> such as persistent cough, phlegm, throat irritation and shortness of breathing since at least three years in their histories. In addition, persons with reduced % FEV<sub>1.0</sub> (under 80 %) with symptoms since less than three years but over one year were included in this category.

Those patients were trained as to check correctly ~~in~~ their symptom-diaries which were prepared by the contractor as shown in Fig. 1 regarding respiratory symptoms and related disorders. They were supervised by the practitioner of the attached Clinic located in the factory and also by the contractor who used to visit there at least once a month. However, at the end of one year's observation, only sixty three patients had completed their diaries correctly; from August 1, 1963 to July 31, 1964.

They were tested their pulmonary function by using Benedict Roth Spirometer at the begin of December, 1964 when same technicians and same apparatus were used as in previous survey at December, 1962. In this occasion, pneumokoniosis patients diagnosed by X-ray film and normal persons were also tested as the control.

Environmental data were obtained from the Kawasaki Municipal Institute Hygiene under kindness of Dr. Terabe, the director of this Institute. The data were such as monthly determination of dust fall in Ton/km<sup>2</sup>/month, and sulfur dioxide mg/day/100cm<sup>2</sup> PbO<sub>2</sub> which were the averages of four spots located around the factory in near distance; i.e. Ohkawa Cho, Ohgi machi, Minami Oda and Kokan-dori.

Besides, daily data such as visibility in km, <sup>daily</sup> mean air flow ~~and~~ m/second, mean index value of suspended particles in the air and mean content (ppm) of sulfur dioxide from the automatical air samplers were presented for use, so that daily correlation between the incidence of symptoms and data of those items was analysed.

### RESULTS

1. The monthly variation of positive rates of respiratory symptoms related to the air pollution.

The symptom-diary was inspected carefully regarding continuous hazard of coughing, phlegm, sneezing and throat irritation per month for all 63 patients who completed their diaries through a year round. All rates of incidences of symptoms and the monthly quantity of dust fall and sulfur dioxide from the air are shown in Table I and Fig. 2.

As shown in Fig. 2, the incidence curves of coughing, sneezing, phlegm and throat irritation were somehow parallel to that of dust fall or sulfur

dioxide during August to March. For clarifying the correlation, the correlation coefficients were calculated and analysed statistically, and results were presented in Table 2 and Fig. 3.

Through statistical analysis, the incidence of sneezing was positively related to the increase of quantity of dust fall on the significant risk of under 5%, and the incidence of phlegm and sneezing were positively related to the increase of quantity of sulfur dioxide only when data were limited in August to March. However, other combinations between them were not correlated significantly.

## 2. Daily correlation of symptoms and air pollution factors.

The daily incidences of phlegm or coughing in the subjected group were followed up and its variations were measured from the daily average of moving fifteen days incidence and evaluated as excess or diminution.<sup>1)</sup> Those daily differences were compared with the data of visibility, mean air flow, mean index of suspended particles in the air and mean content of sulfur dioxide in the air.

The correlation charts are shown in Fig. 4 and Fig. 5. In the column of phlegm and coughing, the monthly changing curves of small lines are indicated as the fifteen days average lines which are standard lines for calculating the daily differences of symptom incidences. This method using fifteen days average is designed for excluding a bias from seasonal variation, social hazard and others.

When the incidence of phlegm, or coughing or the incidence of occurring either phlegm or coughing are compared with the daily index of suspended particles or content of sulfur dioxide, the correlation coefficients between them are as shown in Table 3. As the observation of sulfur dioxide in the air has done only in May and June, data for calculation were 58 in number as shown in Fig. 5.

In this Table 3., the correlation between phlegm and the index of suspended particles was nearly significant and other correlation were failed in getting significance. Accordingly, suspended particles in the air is considered to influence to the severity of chronic bronchitis.

## 3. The change of % FEV<sub>1.0</sub> in the workers of Tokyo-Yokohama area during two years distance of time.

As stated in the introducing paragraph, the patients of chronic bronchitis, pneumokoniosis as well as normal persons were tested in pulmonary function at the begin of December in 1962 and 1964.

During two years of period, some one showed an increase and other showed a decrease on a value of % FEV<sub>1.0</sub>. Accordingly, the difference between the two values of the same person was classified into one of different columns which were divided in every 5 % of difference; i.e. -15 to -10, -10 to -5, -5 to 0, 0 to +5, +5 to +10, +10 to +15% as shown in Fig. 6. and Table 4. In addition, the subjects were also classified separately as chronic bronchitis, pneumokoniosis and normal persons.

When the three distributing curves are compared, the peak of chronic bronchitis and pneumokoniosis are located in the class of -5 to 0 % difference, while the peak of normal persons are in the class of 0 to +5 % difference. According to statistical analysis, Those difference are significant in a risk

level under 10.

This morning, however, the patients were more easily irritated by dust and sulfur dioxide than normal persons during the same period of the day.

#### DISCUSSION

There are many reports concerning the respiratory symptoms related to the air pollution in Japan. In these reports, those of them stated about the frequency of chronic respiratory symptoms such as phlegm, coughing, throat irritation and shortness of breathing and also about their incidences (2,6,7).

According to Spicer et al. and Holland et al., the frequency of respiratory symptoms among various countries are somewhat similar to each other and persistent cough, phlegm and dyspnea are their hazard. The incidence rates in Japan are rather low comparing with western countries, though those three symptoms are also important in Japan.

So far as follow up survey is concerned, there are not so many reports in Japan, only by Fujino (8) and others. In this report, patients of chronic bronchitis were selected from the general population, a factory male workers in Tokyo. These patients of chronic bronchitis are slight cases in symptom but easy to be irritated by dust and sulfur dioxide because they are working in the factory. Therefore, they were chosen for this survey.

The bronchitis patients group of patients improved gradually during the three months of treatment. Accordingly, the tendency of incidence curves declined as shown in Fig. 2. Even in such situation, some correlations were still recognized between the respiratory symptoms and the environmental factors, such as dust fall, suspended particles in the air, sulfurating grade a month or sulfur dioxide content in the air.

Sneezing is a sign of nasal irritation. There was a close correlation between sneezing and dust fall. The result might be explained by the fact that patients of chronic bronchitis were usually sensitive to the irritants in the air, either chemicals or physical stimuli: cold or air flow.

The incidences of sneezing and phlegm are partially related to the increase of sulfur dioxide in the air as monthly determination; August to March. This fact is also considered as important.

Daily difference of incidence of symptoms with the fifteen days average is a indicator of acute pollution by irritants.

The positive correlation between phlegm and suspended particles is considered as important. Even though correlation coefficients are not significant, negative correlation between phlegm and visibility or air flow rate may be explained by the consideration that the latter are inversely related to the volume of suspended particles in the air.

As far as X-ray is concerned, a slight but significant decrease was proved in the chronic bronchitis and pneumoconiosis group in 2 years compared with the result in control normal group.

We have been carrying out further detailed statistical analyses concerning the above-described theme, and the results will be presented in the next report.

#### CONCLUSION

Through the follow up survey on the patient group picked up from the

previous survey, patients of chronic bronchitis were sensitive to the change of air pollutants in the air. Accordingly, the respiratory symptoms are increased in patient group parallel to the increase of air pollutant in the air. Consequently, obstructive disturbance measured by % FEV<sub>1.0</sub> was slightly developed in patient group during two years.

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bronchitis and the environmental factors related to the air pollution.

( 63 cases )

Positive rates of persons having symptoms per month									
Month	Coughing		Phlegm		Sneezing		Throat irritation		Dust fall in Ton/ km <sup>2</sup> /month
	+	%	+	%	+	%	+	%	
1963 Aug.	27	42.9	33	52.4	27	42.9	22	34.9	37.9
Sept.	26	41.3	32	50.8	28	44.4	28	44.4	31.3
Oct.	22	34.9	33	52.4	21	33.3	22	34.9	42.2
Nov.	15	23.8	28	44.4	19	30.2	21	33.3	24.6
Dec.	22	34.9	28	44.4	16	25.4	19	30.2	15.2
1964 Jan.	21	33.3	25	39.7	24	38.1	24	38.1	38.0
Feb.	21	33.3	26	41.3	16	25.4	16	25.4	21.1
Mar.	22	34.9	23	36.5	19	30.2	17	27.0	30.1
Apr.	17	27.0	22	34.9	15	23.8	15	23.8	28.9
May	15	23.8	19	30.2	13	20.6	16	25.4	30.1
Jun.	19	30.2	22	34.9	17	27.0	13	20.6	31.2
Jul.	6	9.5	18	28.6	9	14.3	11	17.5	25.2
Average		30.8		40.9		29.6		29.6	29.6
									3.9

100cm<sup>2</sup> PbO<sub>2</sub>

Sulfur dioxide  
mg/day/  
100cm<sup>2</sup> PbO<sub>2</sub>

Table 2. The correlation coefficients between the monthly incidence of symptoms due to chronic bronchitis and the environmental factors.

Symptoms	Environmental factors	
	Dust fall in Ton/km <sup>2</sup> /month	Sulfur dioxide mg/day/100cm <sup>2</sup> PbO <sub>2</sub>
Coughing	+ 0.309	+ 0.343
Phlegm	+ 0.321	+ 0.480 *
Sneezing	+ 0.579 *	+ 0.4585 *
Throat irritation	+ 0.403	+ 0.276

Note: The values of sulfur dioxide were gained from monthly determination.

\* ..... significant risk under 5%.

\* ..... significant only in group of first 8 months.

Table 3. The correlation coefficients between the daily incidence of symptoms due to chronic bronchitis and the environmental factors.

Symptoms	Environmental factors			
	Visibility (km)	Mean air flow m/sec	Mean index of suspended particles	Sulfur dioxide (PPM)
Coughing	- 0.036	- 0.042	- 0.051	- 0.074
Phlegm	- 0.186	- 0.187	+ <u>0.329</u> *	- 0.164
Either coughing or phlegm	- 0.154	- 0.142	+ 0.226	- 0.214

Table 4. The change of % FEV<sub>1</sub> in the workers of Tokyo Yokohama area during two years distance of time.

Difference of % FEV <sub>1</sub> during 2 years							
	cases	less than - 15%	- 10%	to 0 - 5%	from 0 to + 5%	+ 10%	less than + 15%
Chronic bronchitis	45	3	2	21	13	5	1
Pneumokoniosis	23	1		14	4	3	1
Normal	22		1	3	10	6	2

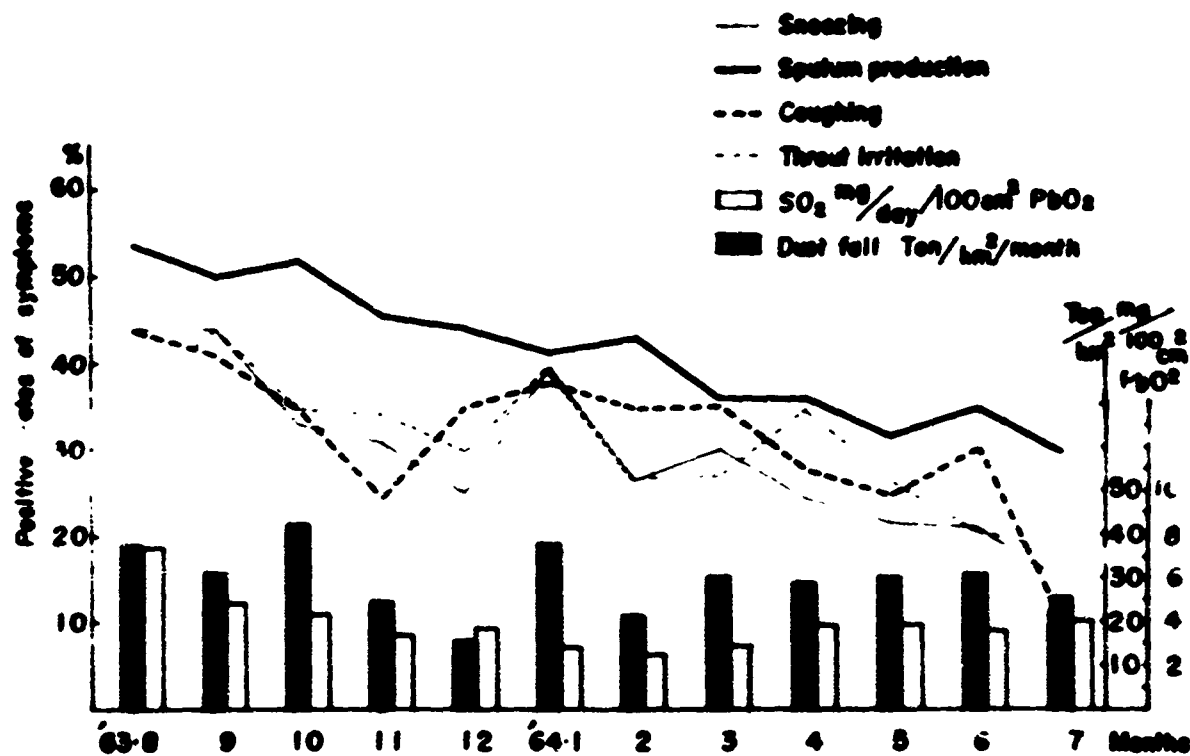
**Fig. 1**

**August. 1963**

**Symptoms Daily**

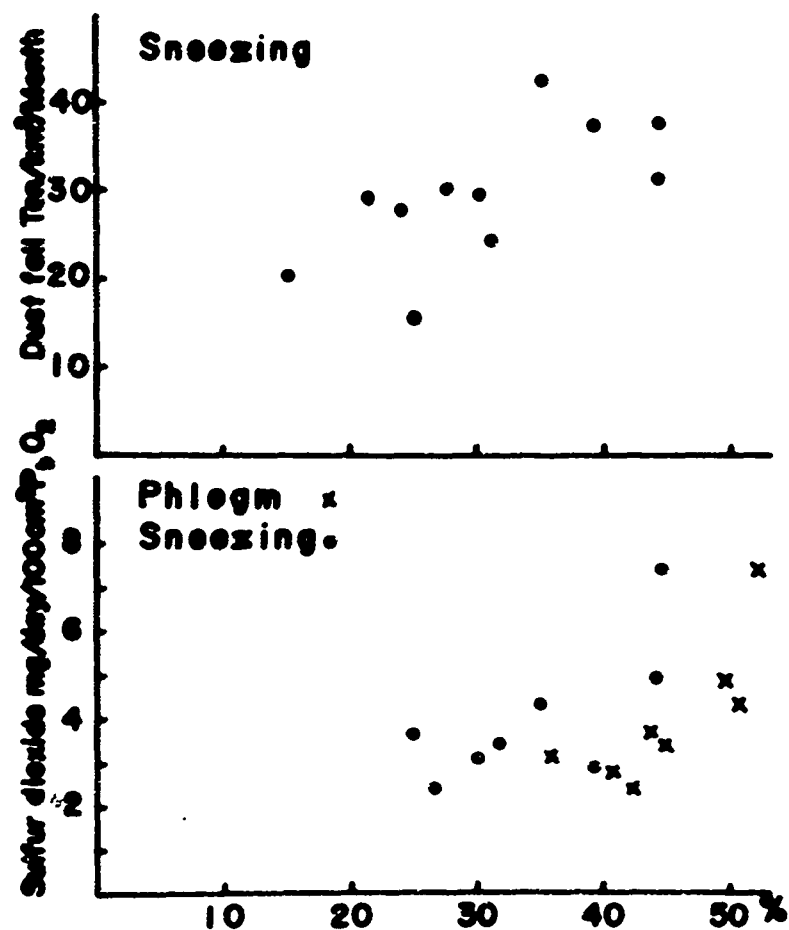
**Name: Yoshino**

<b>Date</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>
<b>Sneezing</b>	○			○			
<b>Rhinorres</b>	○	○	○		○		
<b>Coughing</b>	○	○	○	○	○		
<b>Phlegm</b>	○	○	○	○	○	○	
<b>Throat Irritation</b>			○			○	
<b>Headache</b>	○						
<b>Fever</b>							
<b>Others</b>							



Monthly variations of the positive rates of respiratory symptoms are shown in comparison with dust fall and SO<sub>2</sub> content in the air.

Fig. 2. Monthly Variations of the Positive Rates of Respiratory Symptoms in Comparison with Dust Fall and SO<sub>2</sub> Content in the Air.



**Fig. 3** Correlation between the incidence of symptoms and the monthly change of air pollutants.  
 Notes: Upper chart is during 12 months and lower chart is during 8 months (August to March)

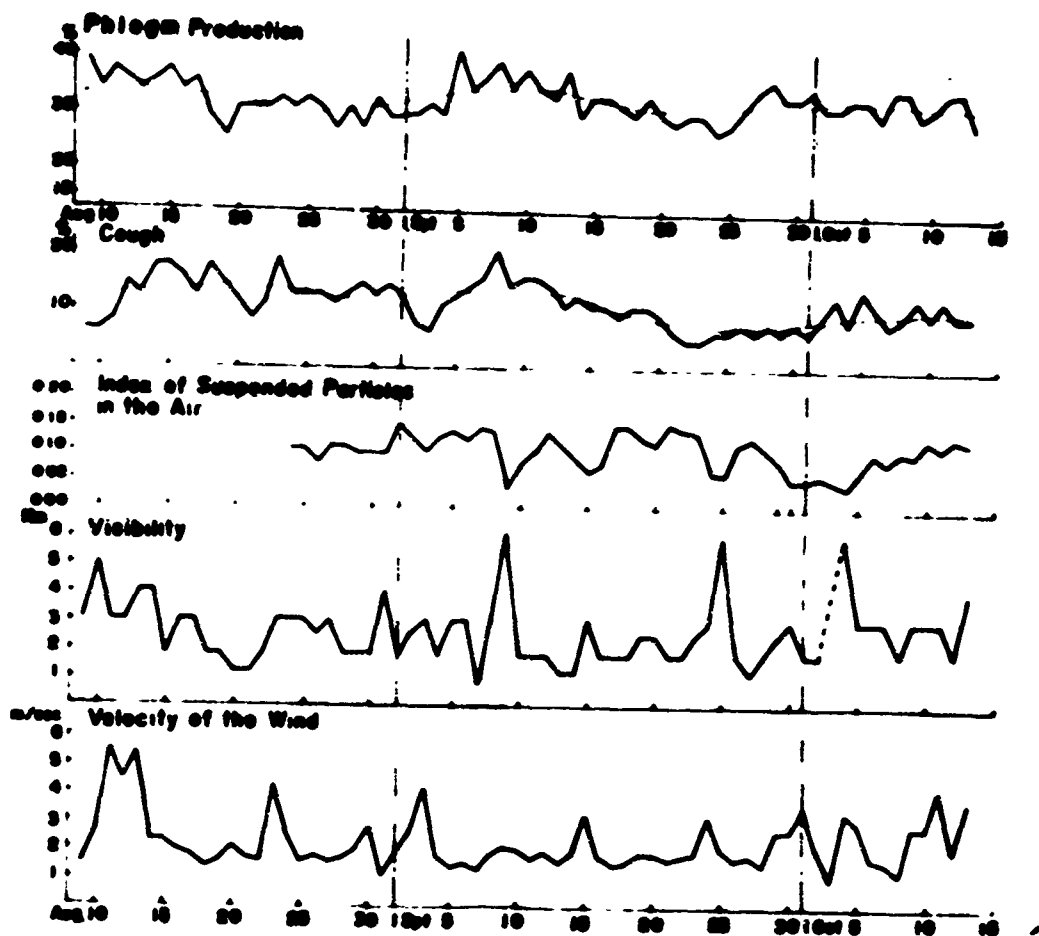


Fig. 4. The Chart of the Daily Incidence Curves of Symptoms as well as the Daily Changes of Environmental Factors Related to the Air Pollution. I



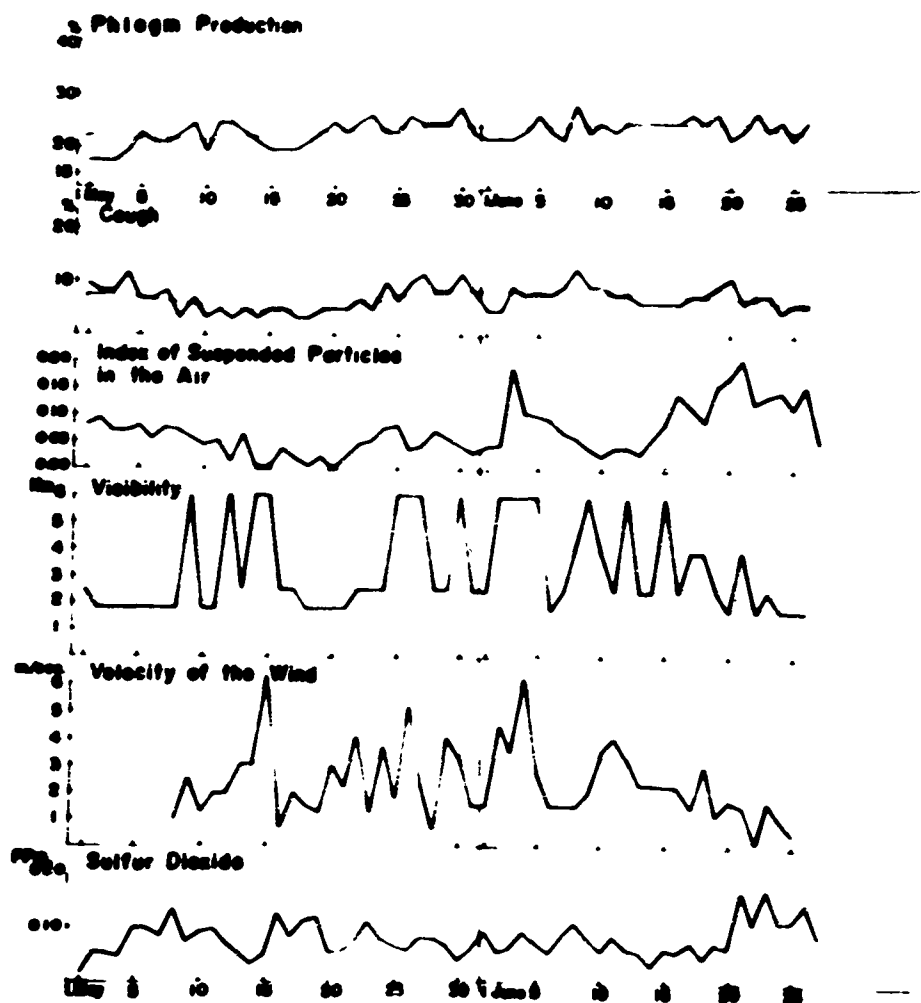


Fig. 5. The Chart of the Daily Incidence Curves of Symptoms as well as the Daily Changes of Environmental Factors Related to the Air Pollution, II.

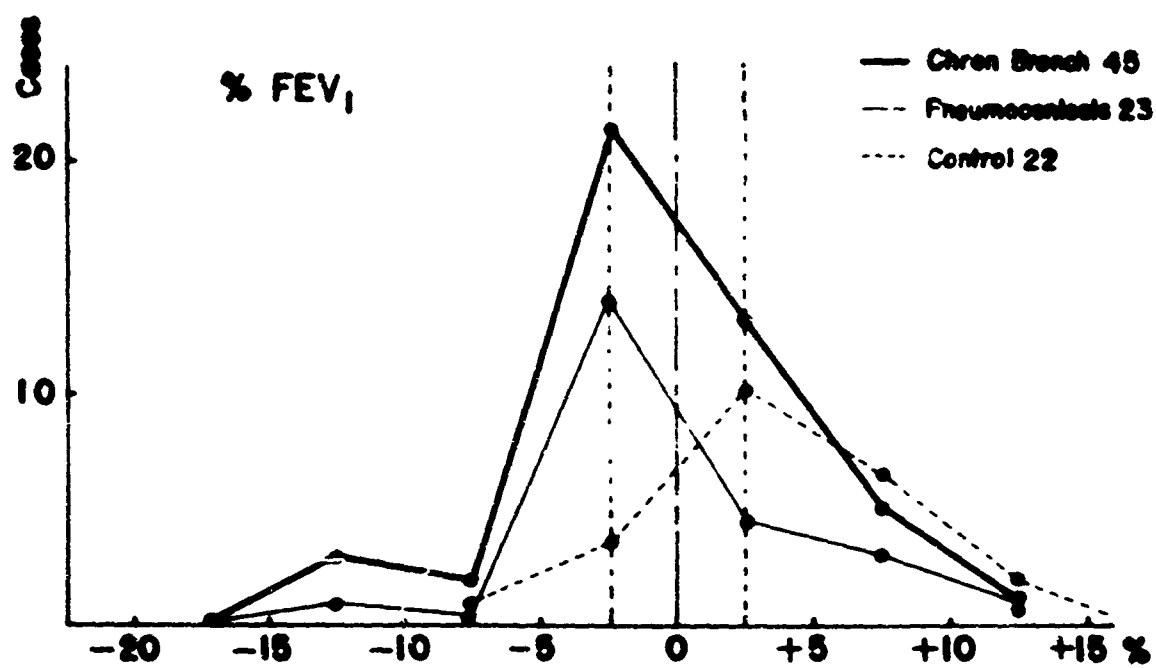


Fig 6. Changes of % FEV<sub>1</sub> in the workers of Tokyo-Yokohama area during two years

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13. ABSTRACT In previous report, we informed that the respiratory symptoms were easily occurred among the people living in Tokyo-Yokohama area and their smoking habits as well as allergic constitution were closely correlated to the onset of such symptoms. This time, main interest was subjected to whether air pollutants, such as sulfur dioxide etc., influence the onset of asthma attack in patients as well as experimental animals. In addition, the respiratory symptoms among the patients of chronic bronchitis were followed up so as to clarify the correlation between the incidence of them and the environmental factors related to the air pollution. The results of investigation are summarized as follows: 1. The influence of sulfur dioxide to guinea pigs was studied on the experimental asthma, measuring the respiratory sensitivity to acetylcholine. Exposures to 30 ppm sulfur dioxide seemed to increase the respiratory sensitivity to acetylcholine, though statistically not significant. 2. Pulmonary diffusing capacity for carbon monoxide was measured among asthmatic patients including similar type to T-Y asthma as well as normal individuals. No significant differences were detected among $D_{LCO}$ of each group. Accordingly, it is suggested that there were no such changes among asthmatic patients including T-Y type as seen in the lung of emphysema or alveo-capillary block. 3. Patients with chronic bronchitis picked up from the previous survey were considered to be sensitive to the changes of air pollutants in the air, since the respiratory symptoms in them increased in parallel with the increase of air pollutants; i.e. dust fall, suspended particles and sulfur dioxide in the air. (Author)		

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Atmosphere pollution Respiratory diseases Acetylcholine sensitivity Sulfur dioxide Plethysmograph Japan						

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